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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,077	09/26/2003	Gunars Valkirs	071949-5407	7483
30542	7590	08/02/2006	EXAMINER	
FOLEY & LARDNER LLP P.O. BOX 80278 SAN DIEGO, CA 92138-0278			COOK, LISA V	
			ART UNIT	PAPER NUMBER

1641

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/673,077

Applicant(s)

VALKIRS ET AL.

Examiner

Lisa V. Cook

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☒ Claim(s) 2-24 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>attached</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Please note that the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all correspondence regarding this application should be directed to Group Art Unit **1641**. All communications should be directed to **Lisa V. Cook**, whose telephone number is **(571) 272-0816**.
2. Claims 1-24 are pending and under consideration.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.
4. The information disclosure statement filed 11/24/04 has been considered as to the merits prior to First Action.
5. The information disclosure statement filed 1/24/05 has been considered as to the merits prior to First Action.
6. The information disclosure statement filed 6/27/05 has been considered as to the merits prior to First Action.
7. The information disclosure statements filed 9/6/05 and 4/24/06 have been considered as to the merits prior to First Action.

Oath/Declaration

8. A new oath or declaration is required because:

I. Non-initialed and/or non-dated alterations have been made to the oath or declaration (See correction to the date for inventor Valkirs and omitted date for inventor Buechler). 37 CFR 1.52(c).

The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

Drawings

9. No drawings were filed in this application.

Specification

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

I. The use of the trademarks has been noted in this application. (.i.e. SEPHAROSE -page 92, and TWEEN-page 94). They should be capitalized wherever they appear and be accompanied by the generic terminology.

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Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Sequence Non-Compliance

11. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

The specification (for example see page 29, page 33-section 0109, page 90, and page 91) recite several sequences but the actual sequence identification numbers are not included. Please provide the appropriate sequence identification numbers in order to comply with the sequence rules.

Applicant is given THREE MONTHS from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Objections

12. Claims 2-24 are objected to under 37 CFR 1.75(c) for the following informalities: The claims are dependent on the method of claim 1, as such they should refer to the previous method by “The”. For example claim 2 should read “The method according to claim 1,”. Appropriate correction is required.

13. Claims 2 and 10 are objected to because of the following informalities: Claims 2 and 10 utilize acronyms (for example see TRAIL, TWEAK, KL-6, etc.). Although the terms may have art-recognized meanings, it is not clear if applicant intends to claim any prior art definition of the abbreviations. The terms should be defined in their first instance. The initial explanation will convey intended meaning of subsequent abbreviations in the claims. Please define in the claims in order to obviate this objection.

14. Claim 24 is objected to under 37 CFR 1.75(c) for the following informality. The term “temoral” is not spelled correctly - it should be spelled “temporal”. Please correct.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

15. Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-24 are vague and indefinite in reciting “subject derived markers” because the phrase is not clearly defined in the disclosure or the claims. It is not clear if applicant intends to mean the markers are produced (derived) from the subject or merely that the markers are found in a subject sample? As recited the metes and bounds cannot be determined. It is suggested that the claims read on the determination of a plurality of markers in a sample in order to obviate this rejection. Please correct.

B. Claims 1-24 recite the phrase “markers related to” and “marker related thereto”, however it is unclear how to define markers that are considered to relate to the recited markers in the claim. The specification does not teach examples of “phrase “markers related to” and “marker related thereto”. The phrase “markers related to” and “marker related thereto” language is vague and indefinite because the characteristics needed to determine whether an unknown could be considered phrase “markers related to” and “marker related thereto” is unknown. The specification neither discloses a definition for phrase “markers related to” and neither “marker related thereto”, nor does it teach a requisite amount of retained qualities needed or characteristics necessary to determine phrase “markers related to” and “marker related thereto”. Therefore the claims are unclear.

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C. Claim 24 is vague and indefinite because it is not clear if applicant intends to mean “temporal” as it relates to brain or head injuries or some other measurement. Please clarify.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-24 are drawn to “markers related to” and “marker related thereto”. The written description is not commensurate in scope with the claims drawn to “markers related to” and “marker related thereto”. Neither the specification nor the claims teach how to define or obtain “markers related to” and “marker related thereto”.

There is no guidance as to what the “markers related to” and “marker related thereto” or how much derivation can occur while retaining the required product characteristics necessary to be considered a “markers related to” and “marker related thereto”, reading on the instant claims. There is no guidance as to what the “markers related to” and “marker related thereto” are or which “markers related to” and “marker related thereto” can or cannot be used in the method being claimed. The specification does not include structural examples of “markers related to” and “marker related thereto”. Thus, the resulting “markers related to” and “marker related thereto” could result in a complexes not taught and enabled by the specification.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The skilled artisan cannot envision the detailed structure of the “markers related to” and “marker related thereto”, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus.

Therefore the full breadth of the claims, do not meet the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 1-4 and 19-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Jackowski (U.S. Patent #6,235,489).

Jackowski discloses method for assessing stroke (brain or temporal change) via the measurement of multiple markers. These markers include calbindin-D, myeline basic protein, S-100 β , and thrombomodulin. The detection of these markers can distinguish and/or differentiate between ischemic and hemorrhagic events. Although the patent is silent with respect to the risk of future cerebral vasospasms this limitation is deemed inherent to the procedures taught by Jackowski because the determination that the patient's markers are indicative of an ischemic event would necessarily rule out vasospasms (or subarachnoid hemorrhage). See abstract, figure 2, and column 3-4, for example.

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II. Claims 1-4 and 19-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Jackowski (WO 00/52476).

Jackowski discloses method for assessing stroke (brain or temporal change) via the measurement of multiple markers. These markers include calbindin-D, myeline basic protein, S-100 β , and thrombomodulin. The detection of these markers can distinguish and/or differentiate between ischemic and hemorrhagic events. Although the patent is silent with respect to the risk of future cerebral vasospasms this limitation is deemed inherent to the procedures taught by Jackowski because the determination that the patient's markers are indicative of an ischemic event would necessarily rule out vasospasms (or subarachnoid hemorrhage). See page 2 lines 11-22 and figure 2/6, for example.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

III. Claims 6-8, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being obvious over Jackowski (U.S. Patent #6,235,489) or Jackowski (WO 00/52476) in view of Yakovlev et al. (The Journal of Neuroscience, October 1, 1997, 17(19), pages 7415-7424).

Please see Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) as set forth above.

Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) differ from the instant invention in not specifically teaching the detection of the marker caspase-3.

However, Yakovlev et al. disclose methods to determine caspase-3 in temporal profiles of apoptosis after brain injury. See abstract. Caspase-3 levels were elevated in brain injury and the inhibition of caspase-3 markedly attenuated apoptosis induced by TBI in vivo and improved neurological recovery. See page 7422, 2nd column. These results may prove the basis for new therapeutic treatments of CNS injury. See page 7423.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate caspase-3 as taught by Yakovlev et al. in the method of Jackowski (U.S. Patent #6,235,489) or Jackowski (WO 00/52476) because Yakovlev et al. taught that caspase-3 levels were elevated in brain injury and the inhibition of caspase-3 markedly attenuated apoptosis induced by TBI in vivo and improved neurological recovery. See page 7422, 2nd column. These results may prove the basis for new therapeutic treatments of CNS injury. See page 7423.

IV. Claim 5 is rejected under 35 U.S.C. 103(a) as being obvious over Jackowski (U.S. Patent #6,235,489) or Jackowski (WO 00/52476) in view of Ronn et al. (WO 00/18801).

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Please see Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) as set forth above.

Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) differ from the instant invention in not specifically teaching the detection of NCAM or neural cell adhesion molecule.

However, Ronn et al. disclose methods to determine and assess the NCAM marker. See abstract, page 16 lines 8-31, and page 34 lines 11-28. The marker is useful in the evaluation of several disorders including stroke. Absent evidence to the contrary, it would have been obvious to one of ordinary skill in the art to employ the marker NCAM to assess stroke because the prior art has established the relationship between NCAM and stroke. See WO 00/52476 to Ronn et al.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use NCAM as a marker for stroke, since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

V. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being obvious over Jackowski (U.S. Patent #6,235,489) or Jackowski (WO 00/52476) in view of Greenberg (Drug News and Perspectives, 1998, Vol.11, No.5, pages 265-270. Abstract Only).

Please see Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) as set forth above.

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Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) differ from the instant invention in not specifically teaching the detection of the marker VEGF.

However, Greenberg discloses that stroke results from focal cerebral ischemia due to the occlusion of cerebral blood vessels (angiogenesis). Greenberg further teaches that VEGF is a key mediator of angiogenesis and cerebral ischemia. The understanding of VEGF may have implications for prognosis and treatment in stroke. See abstract.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate VEGF as taught by Greenberg in the method of Jackowski (U.S. Patent #6,235,489) or Jackowski (WO 00/52476) because Greenberg taught that that VEGF is a key mediator of angiogenesis and cerebral ischemia. The understanding of VEGF may have implications for prognosis and treatment in stroke. See abstract.

VI. Claims 12-14 and 16 are rejected under 35 U.S.C. 103(a) as being obvious over Jackowski (U.S. Patent #6,235,489) or Jackowski (WO 00/52476) in view of Roger et al. (Journal of the American College of Cardiology, 1999, Vol.34, No.1, pages 155-162).

Please see Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) as set forth above.

Jackowski (U.S. Patent #6,235,489) and Jackowski (WO 00/52476) differ from the instant invention in not specifically teaching the detection of the detection of a marker relating to blood pressure, such as BNP (B-type natriuretic peptide) or brain natriuretic peptide.

However, Roger et al. disclose methods measuring BNP and its effects on hemodynamics. BNP is elevated in patients with heart failure, and serves as a sensitive and specific serologic marker for left ventricle dysfunction. BNP is disclosed as a component in the

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modulation of cardiac and vascular function and fluid status. See page 155. The studies included stroke patients. See Table 1 on page 156. The measurement and monitoring of BNP was found useful in the assessment of the drug nesiritide. See 161.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate BNP as taught by Roger et al. in the method of Jackowski (U.S. Patent #6,235,489) or Jackowski (WO 00/52476) because Roger et al. taught that BNP is a component in the modulation of cardiac, vascular function, and fluid status. See page 155. Since stroke and vasospasms are related to blood vessel flow, one of ordinary skill in the art would have evaluated BNP in order to monitor blood flow as it relates to these disorders.

19. For reasons aforementioned, no claims are allowed.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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